CHRONIC LYMPHOCYTIC LEUKEMIA

Treatment

Early-Stage Disease

Since patients with early-stage chronic lymphocytic leukemia (CLL) have a good long-term prognosis, and therapy has not changed the outcome of the disease, patients in the early stages should not be treated unless specific indications exist (Table 1).

TABLE 1: Suggested indications for therapy in early-stage CLL

Progressive disease-related symptoms (eg, fever, night sweats, weight loss)
Bone marrow involvement with progressive anemia and thrombocytopenia
Progressive or painful splenomegaly
Progressive or bulky lymphadenopathy
Rapidly increasing lymphocytosis
Autoimmune hemolytic anemia or thrombocytopenia
Increased frequency of bacterial infections

Conventional Chemotherapy

Single-Agent Chemotherapy

Chlorambucil: The most frequently used single agent for CLL is chlorambucil (Leukeran), given as either 0.1 mg/kg daily or 0.4 to 1.0 mg/kg every 4 weeks. The daily schedule may be superior, probably because the total dose given is higher, but the monthly schedule is still widely used. Therapy is continued until the signs or symptoms requiring therapy are controlled.

Chlorambucil is frequently combined with oral prednisone (30 to 100 mg/m²/d), although there is no clear evidence that the combination improves responses or overall survival over chlorambucil alone. Prednisone is of value, however, in the management of autoimmune cytopenias. High-dose chlorambucil therapy may be associated with a higher response rate and longer survival time.

Cyclophosphamide is an alternative to chlorambucil. The usual dose is 1 to 2 g/m² every 3 to 4 weeks together with vincristine and steroids (eg, COP regimen; see below).

Combination Chemotherapy

COP and CHOP: Various drug combinations have been used in CLL, mostly in patients with advanced-stage disease. The most frequently employed combinations have been cyclophosphamide, Oncovin, and prednisone (COP), and these three drugs plus doxorubicin (CHOP). The dose of doxorubicin used is usually low (25 mg/m²). A higher dose of doxorubicin (50 mg/m²) has been employed in some regimens, such as CAP (cyclophosphamide, Adriamycin, and prednisone).

Response rates have been 40% to 85% with these combinations. In randomized studies, COP was no better than chlorambucil and prednisone. Although CHOP initially achieved better survival than COP (in Binet stage C) or chlorambucil plus prednisone, longer follow-up has not confirmed this survival advantage. Similarly, other chemotherapy combinations have failed to improve on the results attainable with simpler regimens.

New Approaches

Nucleoside Analogs

Fludarabine (Fludara) is the most promising new agent for the treatment of CLL. When given to previously treated patients at a dose of 25 to 30 mg/m²/d for 5 days every 3 to 4 weeks, this nucleoside analog produced responses in approximately 50% of patients, with 30% of patients achieving a CR or "nodular CR," ie, a CR but with the presence of lymphoid nodules in the bone marrow (Table 2).

TABLE 2: Response criteria in CLL according to the International Workshop on CLL (IWCLL)

Complete response
Resolution of lymphadenopathy, splenomegaly, hepatomegaly, and constitutional symptoms Normalization of blood counts Neutrophils > 1,500/µL Platelets > 100,000/µL Lymphocytes < 4,000/µL Normalization of bone marrow < 30% lymphocytes[1] Nodular or focal infiltrates[2]
Partial response
Downstaging (from Binet stages C to A or B, and from B to A)[2] *or* > 50% decrease in absolute lymphocyte count, splenomegaly, lymphadenopathy, hepatomegaly, neutrophils greater than or equal to 1,500/µL, platelets greater than or equal to 100,000/µL, hemoglobin > 11 g/dL, or > 50% improvement in peripheral blood counts[1]
[1]National Cancer Institute Criteria [2]IWCLL Criteria

In previously untreated patients, the response rate was about 80%, with 60% of patients achieving a CR or nodular CR.

One study of CLL patients refractory to fludarabine found that four consecutive such patients responded to 2-CdA (Leustatin), one of whom achieved a CR (*Juliusson G, Elmborn-Rosenberg A, Liliemark J: N Engl J Med 327:1056–1061, 1992).* Subsequent studies suggested cross-resistance between these two agents. In the largest series, O'Brien et al treated 28 CLL patients refractory to fludarabine with 2-CdA and observed only 2 partial responses and no CRs *(O'Brien S, Kantarjian H, Estey E: N Engl J Med 330:319–322; 1994).*

The addition of prednisone to fludarabine therapy has not improved the response rate but was associated with an increased incidence of opportunistic infections, including *Pneumocystis carinii* pneumonia and *Listeria* sepsis or meningitis. Randomized studies comparing fludarabine to CAP or CHOP have shown increased response rates with fludarabine, but longer follow-up is needed to determine the drug's impact on survival (Table 3).

TABLE 3: Comparison of fludarabine, CAP, and CHOP treatment for CLL

	Response rate (%)		
Patient characteristics	**Fludarabine**	**CAP**	**CHOP**
All	58	42	NA

Untreated	45	26	NA
Previously treated	70	58	NA
Stage B (Binet)	94	72	75
Stage C (Binet)	64	84	62

NA = Results not available
CAP = Cyclophosphamide, Adriamycin, prednisone
CHOP = Cyclophosphamide, doxorubicin HCl, Oncovin, prednisone

Other nucleoside analogs: 2-Chlorodeoxyadenosine (2-CdA {Leustatin]) is also active in CLL when given at doses of 0.1 mg/kg/d (or 4 mg/m²/d) for 7 days. The CR rate with this drug may be lower than with fludarabine, but a direct comparison has not been reported. Another nucleoside analog, 2-deoxycoformycin (Nipent), has little activity in CLL.

Bone Marrow Transplantation

Both allogeneic and autologous BMT have produced some encouraging results in patients with CLL. The role of marrow transplantation in CLL deserves further investigation in a research setting.

In one series, 38% of bone marrow transplant patients experienced greater than or equal to grade 2 acute GVHD and 47% had chronic GVHD *(Michallet M, Archimbaud E, Bandini G, et al: Blood 82:346a, 1993).* In contrast, in two other series involving a total of 19 patients, only one severe acute and one chronic GVHD episode occurred *(Rabinowe SN, Soiffer RJ, Gribben JG, et al: Blood 82:1366–1376, 1993; Khouri IF, Keating MJ, Vriesendorp H: J Clin Oncol 12:748, 1994).* The major difference among the three studies is the use of fludarabine in nearly all patients in the two later studies, compared to none in the first trial. Fludarabine may impair the presentation and/or recognition of self-antigens by the graft

Allogeneic BMT is a viable option for younger patients with CLL, particularly if they have failed to respond to alkylating agent and/or nucleoside analog therapy, and are in advanced CLL stages. The series reported to date, including a majority of patients with advanced, refractory disease, have documented a CR rate in excess of 70%. The response is sustained in most patients, although follow-up is still short.

Autologous BMT: Since the median age of CLL patients is usually higher than the age considered acceptable for allogeneic BMT, autologous transplants using purged marrow have also been investigated. Some CRs have been obtained and maintained for at least 10 months.

Biologic response modifiers: IFN-alfa can induce some response in untreated patients with early-stage disease, and its role in prolonging chemotherapy-induced responses is under investigation. IL-2 has been used with little success.

Monoclonal antibody-targeted therapy: Monoclonal antibodies (MoAbs) have been used in CLL in an attempt to exploit antibody-mediated cytotoxicity, but have been minimally successful. Although conjugation of MoAbs to toxins (eg, ricin, diphtheria toxin) or radioactive isotopes (iodine-131) has produced some encouraging results, more experience with this approach is required.

Splenectomy: Splenectomy may be beneficial for patients in whom hypersplenism is believed to be the cause of cytopenias, or for palliation when splenomegaly is symptomatic and refractory to treatment with chemotherapy. Cytopenias respond to splenectomy, which is associated with minimal mortality.

Radiotherapy: TBI with a low fraction size of 15 cGy, to total doses of 75 to 150 cGy, has been used in the treatment of CLL. Approximately one-third of patients achieve a complete response. The median survival of CLL patients treated with TBI is nearly 5 years.

Treatment Recommendations

Based on current knowledge, conventional chemotherapy with chlorambucil, with or without prednisone, appears to be as good as any combination, and should be used initially for patients not enrolled in clinical trials. Second-line therapy includes nucleoside analogs and allogeneic or autologous BMT. Enough data may accumulate soon to suggest the use of nucleoside analogs in front-line CLL therapy.

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